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Association Between Frequency of Atrial and Ventricular Ectopic Beats and Biventricular Pacing Percentage and Outcomes in Patients With Cardiac Resynchronization Therapy

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ABSTRACT

BACKGROUND A high percentage of biventricular pacing is required for optimal outcome in patients treated with cardiac resynchronization therapy (CRT), but the influence of ectopic beats on the success of biventricular pacing has not been well established.

OBJECTIVES This study sought to determine if increased ectopic beats reduce the chance of high biventricular pacing percentage and are associated with subsequent adverse outcomes.

METHODS From the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy), 801 patients with an implanted CRT-defibrillator device with data available on biventricular pacing percentage and pre-implantation 24-h Holter recordings were included. Using logistic regression, we estimated the influence of ectopic beats on the percentage of biventricular pacing. Reverse remodeling was measured as reductions in atrial and left ventricular end-systolic volumes (LVESV) at 1 year. Cox models were used to assess the influence of ectopic beats on the outcomes of heart failure (HF) or death, ventricular tachyarrhythmias (VTAs), and death.

RESULTS In the pre-implantation Holter recording, ectopic beats accounted for a mean 3.2 ± 5.5% of all beats. The probability of subsequent low biventricular pacing percentage (<97%) was increased 3-fold (odds ratio: 3.37; 95% confidence interval: 1.74 to 6.50; $p < 0.001$) in patients with 0.1% to 1.5% ectopic beats and 13-fold (odds ratio: 13.42; 95% confidence interval: 7.02 to 25.66; $p < 0.001$) in patients with >1.5% ectopic beats compared with those with <0.1% ectopic beats. Patients with ≥0.1% ectopic beats had significantly less reverse remodeling (percent reduction in LVESV 31 ± 15%) than patients with <0.1% ectopic beats (percent reduction in LVESV 39 ± 14%; $p < 0.001$). The risk of HF/death and VTA was increased significantly in those with 0.1% to 1.5% ectopic beats (hazard ratio: 3.13 and 1.84, respectively) and for >1.5% ectopic beats (hazard ratio: 2.38 and 2.74, respectively).

CONCLUSIONS Relatively low frequencies of ectopic beats (≥0.1%) dramatically increase the probability of low biventricular pacing (<97%), with reduced CRT efficacy by less reverse remodeling and higher risk of HF/death and VTA. This supports pre-implantation Holter monitoring of patients selected for CRT for optimal outcome. (MADIT-CRT: Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy; NCT00180271)
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ABBREVIATIONS AND ACRONYMS

APC = atrial premature complex

CRT-D = cardiac resynchronization therapy with implantable cardioverter-defibrillator

HF = heart failure

HR = hazard ratio

LBBB = left bundle branch block

NYHA = New York Heart Association

PVC = premature ventricular complex

VTA = ventricular tachyarrhythmia

Cardiac resynchronization therapy (CRT) in heart failure (HF) patients with left ventricular dysfunction and a wide QRS duration has been shown to reduce mortality and improve HF symptoms (1,2). The margin of success associated with implantation of a CRT device, however, relies on the capability to effectively deliver biventricular pacing, and even minor reductions in biventricular pacing can diminish the beneficial effects of CRT (3–8).

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Ventricular ectopy (isolated premature ventricular complexes [PVCs] or nonsustained ventricular tachycardia) may preclude the delivery of 100% effective biventricular pacing and thus compromise symptomatic response and left ventricular reverse remodeling after implantation with a CRT device (9). Recently, it was shown that atrial premature complexes (APCs) may play a significant role in loss of optimal biventricular pacing percentage in patients who receive CRT (10). It is important to select the right patients for CRT implantation who will respond to the therapy and to identify those who may respond suboptimally, to initiate other treatments or closer follow-up. A 24-h Holter recording is an inexpensive and effective method of acquiring accurate data on both APCs and PVCs; however, limited data exist regarding the prognostic significance of preimplantation Holter-detected atrial and ventricular premature beats in patients undergoing CRT implantation. Therefore, we sought to determine whether the frequency of premature atrial and ventricular ectopic beats influenced optimal biventricular pacing percentage and reflected reverse remodeling and clinical events in those patients who were treated with CRT with an implantable cardioverter-defibrillator (CRT-D) in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy).

METHODS

The protocol and primary results of the MADIT-CRT study were published previously (1,11). During the period 2004 to 2009, we included 1,820 patients with left ventricular ejection fraction ≤30%, QRS duration ≥130 ms, and ischemic cardiomyopathy of New York Heart Association (NYHA) functional class I or II or nonischemic cardiomyopathy of NYHA functional class II. Patients were enrolled from 110 centers in Europe, Canada, and the United States and randomized in a 3:2 fashion for CRT-D (n = 1,089) or implantable cardioverter-defibrillator (ICD) devices (n = 731). Patients were in sinus rhythm at enrollment and were excluded if they had experienced atrial arrhythmia within 1 month before enrollment, although a prior history of atrial fibrillation was not an exclusion criterion.

STUDY POPULATION. For this study, we analyzed patients who were randomized to CRT-D, had a preimplantation Holter recording performed, had an average biventricular pacing percentage reading at the latest possible follow-up, and had interrogation of the device (n = 801). For echocardiographic measurements and changes at 1-year follow-up, we evaluated the changes in 609 patients who also had paired baseline and 1-year echocardiograms. **Figure 1** shows the exact definitions and flow diagram of the study population. The Institutional Review Board approved the protocol at each participating organization, and each patient provided written informed consent before enrollment.

Patients assigned to CRT-D underwent 24-h 12-lead Holter monitoring before implantation. Mortara H12 recorders were used, and data were analyzed by an

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electrocardiography core laboratory using a Mortara H-Scribe scanning system (Mortara Instruments, Milwaukee, Wisconsin). The automatically derived annotation of beats was verified for quality by technicians who were blinded to the data, and data were used to quantify monitoring period, total beats during monitoring period, total APCs, and total PVCs. A run of either APCs or PVCs was defined as 3 consecutive beats or more. The number of APCs and PVCs combined were then divided by the total number of beats for a measure of *ectopic burden* in percentage of ectopic beats of all beats. The ectopic burden was then defined by the distribution in percentiles in 3 predefined major groups. The first group (low/very low ectopic burden) was defined as the lowest quintile (0 to 20th percentiles), the second group (moderate ectopic burden) was defined as the 2 middle quintiles (21st to 60th percentiles), and the third group (high ectopic burden) was defined as the 2 upper quintiles (61st to 100th percentiles). These groups translated into <0.1% ectopic beats, 0.1% to 1.5% ectopic beats, and >1.5% ectopic beats, respectively (Figure 1). For supplementary and sensitivity analysis, we further performed all analyses on the basis of the distribution by quartiles and quintiles.

DEVICE PROGRAMMING AND INTERROGATION. Commercially available devices from Boston Scientific were used in this trial, the programming for which has been described in the pre-specified protocol (11). All devices were interrogated 1 month after enrollment and every 3 months thereafter. All interrogation discs were sent to an independent core laboratory for final adjudication and interpretation. The biventricular pacing percentage was determined as the average delivery of biventricular pacing percentage throughout the follow-up time at the last available device interrogation. Two groups were selected as representing high (≥97%) and low (<97%) biventricular pacing, on the basis of a recent literature review and results from the MADIT-CRT trial evaluating the cutoff point of biventricular pacing efficacy on HF/death and death (5,8,12).

ECHOCARDIOGRAPHY. Echocardiography was performed before implantation and at 1-year follow-up according to the study protocol. All echocardiograms were evaluated and measured by the core echocardiography laboratory by use of standardized methods as defined in the protocol. Different levels of percentage left atrial volume (LAV), left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume reduction from baseline to 1-year follow-up were used to evaluate reverse remodeling of CRT patients according to the percentage of ectopic beats.

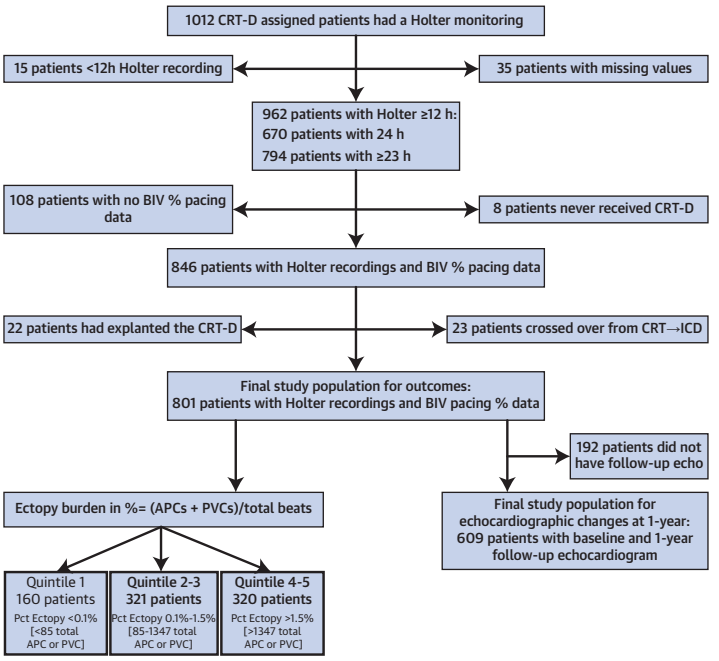


FIGURE 1 Study Population Flow Chart

This flow chart shows the study population of the group with cardiac resynchronization therapy with implantable cardioverter-defibrillator (CRT-D) from the MADIT-CRT study and the distribution of patients in 3 groups by ectopic burden as measured by pre-implantation Holter monitoring. APC = atrial premature complex; BIV = biventricular; ICD = implantable cardioverter-defibrillator; Pct = percent; PVC = premature ventricular complex.

A reverse remodeling echocardiographic super-response was defined as the proportion with changes with >30% reduction in LVESV.

ENDPOINTS. The primary endpoint of the present study was defined as death of any cause or nonfatal HF events, whichever came first. The diagnosis of HF required symptoms consistent with congestive HF, response to intravenous decongestive therapy for outpatients, and either oral or intravenous decongestive therapy for patients in the hospital. A mortality committee unaware of study group assignments independently adjudicated the diagnosis (11). The secondary endpoint was malignant ventricular tachyarrhythmias (VTAs), defined as appropriate ICD therapy for ventricular tachycardia or ventricular fibrillation, delivered as either antitachycardia pacing or shock. VTAs were adjudicated blindly as described previously (13). The tertiary endpoint was all-cause mortality.

STATISTICAL ANALYSIS. For comparison of baseline variables among the 3 groups, we used chi-square test or Fisher exact test for categorical variables and

TABLE 1 Baseline Clinical Parameters

	Percent Ectopy <0.1%	Percent Ectopy 0.1% to 1.5%	p Value*	Percent Ectopy >1.5%	p Value†	Overall p Value for Comparisons
Patients	160 (20)	321 (40)		320 (40)		<0.001
Female	69 (43)	83 (26)	<0.001	46 (14)	<0.001	<0.001
Age at enrollment, yrs	59.5 ± 11.2	64.9 ± 10.0	<0.001	66.8 ± 9.8	0.022	<0.001
Cardiac history						
Ischemic NYHA functional class I	12 (8)	42 (13)	0.068	49 (15)	0.419	0.054
Ischemic NYHA functional class II	48 (30)	140 (44)	0.004	147 (46)	0.554	0.003
Nonischemic NYHA functional class II	100 (63)	139 (43)	<0.001	147 (46)	0.241	0.054
Diabetes	50 (31)	89 (28)	0.422	109 (34)	0.083	0.221
Hypertension	86 (54)	211 (66)	0.008	209 (65)	0.825	0.019
Prior CABG revascularization	21 (13)	90 (28)	<0.001	111 (35)	0.070	<0.001
Prior myocardial infarction	43 (27)	148 (47)	<0.001	149 (48)	0.876	<0.001
Prior atrial arrhythmias	11 (7)	40 (13)	0.063	37 (12)	0.795	0.167
Prior ventricular arrhythmias	6 (4)	24 (8)	0.111	29 (9)	0.444	0.103
Medications						
Antiarrhythmic agent, including amiodarone and sotalol	8 (5)	34 (11)	0.041	25 (8)	0.224	0.102
ACE inhibitor or ARB	156 (98)	310 (97)	0.782	303 (95)	0.243	0.266
Aldosterone antagonist	50 (31)	109 (34)	0.552	96 (30)	0.283	0.552
Beta-blockers	154 (96)	300 (93)	0.210	291 (91)	0.234	0.091
Statins	98 (61)	221 (69)	0.097	234 (73)	0.233	0.030
Clinical characteristics at enrollment						
QRS duration, ms	162.0 ± 17.4	159.3 ± 19.5	0.074	155.7 ± 19.8	0.010	<0.001
LBBB	136 (85)	242 (75)	0.015	198 (62)	<0.001	<0.001
RBBB	8 (5)	33 (10)	0.051	56 (18)	0.008	<0.001
Heart rate, beats/min	68.7 ± 10.5	67.5 ± 10.7	0.133	67.0 ± 10.5	0.539	0.140
Creatinine, mg/dl	1.09 ± 0.33	1.14 ± 0.32	0.050	1.19 ± 0.31	0.014	<0.001
Echocardiographic characteristics at enrollment						
LVEF, %	29.4 ± 3.5	29.0 ± 3.5	0.135	29.0 ± 3.1	0.972	0.256
LVEDV indexed by BSA	119.1 ± 24.4	124.1 ± 26.6	0.030	123.3 ± 26.6	0.601	0.076
LVESV indexed by BSA	84.4 ± 19.7	88.6 ± 21.7	0.023	87.8 ± 21.3	0.587	0.058
LAV indexed by BSA	43.6 ± 8.9	46.9 ± 9.9	<0.001	46.7 ± 9.8	0.711	<0.001
Holter monitoring and BIV pace interrogation						
BIV pacing ≥97%	148 (93)	250 (78)	<0.001	147 (46)	<0.001	<0.001
APC total	6 (2-16)	27 (8-77)	<0.001	95 (20-787)	<0.001	<0.001
PVC total	16 (6-31)	255 (120-572)	<0.001	3,593 (2,436-9,242)	<0.001	<0.001
Runs of PVCs ≥1	18 (11)	134 (42)	<0.001	243 (76)	<0.001	<0.001
Runs of PVCs ≥10	0 (0)	5 (2)	0.175	85 (27)	<0.001	<0.001

Values are n (%), mean ± SD, or median (interquartile range). *p value compares percent ectopy <0.1% with percent ectopy 0.1% to 1.5%. †p value compares percent ectopy 0.1% to 1.5% with percent ectopy >1.5%.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; APC = atrial premature complex; BIV = biventricular; BSA = body surface area; CABG = coronary artery bypass graft; LAV = left atrial volume; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; PVC = premature ventricular complex; RBBB = right bundle branch block.

the Kruskal-Wallis test for continuous variables. Variables distributed in a non-Gaussian way were reported with median values (interquartile ranges), whereas those with a Gaussian distribution were reported as mean ± SD.

Several models were used for analyses in this study. We used logistic regression models to estimate the likelihood of receiving a low biventricular pacing percentage (defined as <97%) versus a high biventricular pacing percentage (defined as ≥97%). We used a stepwise selection of variables that had a significant ($p < 0.05$) association with low biventricular pacing and adjusted for these variables along with those a priori thought to be associated with unfavorable and low biventricular pacing, which were forced in the model. Separate models evaluated the influence of ectopic beats by ectopic burden groups, as a continuous variable, and by 0.1% increments using an ordinal scale from 0% to 1.5%, with patients with >1.5% ectopic beats pooled together.

Echocardiographic measurements and evaluation from baseline to 1-year follow-up were compared among the 3 ectopic burden groups with an analysis of variance if a Gaussian distribution was present

for the continuous covariates, or the Kruskal-Wallis test was used, whereas a chi-square test was used for the categorical covariates. We used 2 Cox proportional hazard regression models to evaluate the influence of percentage of ectopic burden on the endpoint of HF or death, VTA, and all-cause mortality. These models were adjusted for covariates found by stepwise selection from the pool of available covariates and included if significant ($p < 0.05$) or if thought to be relevant to the outcome a priori and then forced into the model. The covariates used in the models are listed below the Tables. Again, we used the lowest quintile of ectopy as the reference group. For the all-cause mortality model, we selected 6 covariates for adjustment despite only 33 deaths, which potentially resulted in a slightly overfitted model.

Odds ratios (ORs) and hazard ratios with their 95% confidence intervals (CIs) and 2-sided p values are reported. The cumulative probability of HF or death was displayed by the method of Kaplan-Meier using the log-rank test to compare cumulative events. A 2-tailed p value <0.05 was considered statistically significant. Analyses were performed with the SAS version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 801 patients were monitored by preimplantation Holter and received CRT-D. Mean Holter recording time was 23.2 ± 1.7 h. The amounts of APCs (mean 516 ± 2,100 beats) and PVCs (mean 2,487 ± 4,725 beats) were distributed in a skewed fashion, with most patients having low numbers of APCs (median 28 [8 to 11]) and PVCs (median 490 [77 to 2,509]). The mean number of beats measured during Holter monitoring was normally distributed in the population (94,209 ± 14,579 beats). Ectopic beats accounted for a mean of 3.2 ± 0.8% of all beats, mostly dominated by PVCs (Table 1). Seventy-six patients (9.5%) had 10% or more ectopic beats. Nearly one-half of the patients (49%) experienced at least 1 run of PVCs, and 11% had >10 runs. A minor proportion (15%) had at least 1 run of APCs, and 4% had >10 runs of APCs. Four patients had runs of APCs of >30 consecutive beats, none of these had evidence of paroxysmal atrial fibrillation, and were regular runs of supraventricular tachycardia during the Holter recording. We created 3 ectopic burden groups: <0.1%, 0.1% to 1.5%, and >1.5% ectopic beats (as a percentage of all beats).

Table 1 shows the comparison of baseline characteristics of the 3 groups. In general, those patients who had higher percentages of ectopic beats had more advanced cardiac disease than those with <0.1% ectopic beats, as represented by higher proportions of ischemic cardiomyopathy, hypertension, and prior coronary artery bypass grafting, whereas there was no significant difference in reported past atrial or ventricular arrhythmias. At baseline, the patients received the same proportions of medications, except for a greater use of statins in the 2 upper ectopic groups. These patients more frequently had non-left bundle branch block (LBBB) QRS configuration, shorter QRS durations, and slightly larger ventricular and atrial volumes.

The likelihood of receiving low biventricular pacing (defined as <97%) was raised with increasing burden of ectopic beats at baseline (Figures 2 and 3). The probability of low biventricular pacing was increased by 18% per percent increase in ectopic beats (OR: 1.18; 95% CI: 1.14 to 1.23; $p < 0.001$). There was a stepwise significantly higher probability of low pacing with increasing percentage of ectopic beats, as illustrated in Figure 3. Table 2 shows that the likelihood of low biventricular pacing in those with ectopic beats >1.5% was 13-fold higher than in those with <0.1% ectopic beats (OR: 13.42; 95% CI: 7.02 to 25.66; $p < 0.001$). The addition of ectopic burden to the multivariate model increased the C statistic from 0.64 to 0.78. Likewise, the probability of low pacing was almost 7-fold higher in those with ≥0.1% ectopic

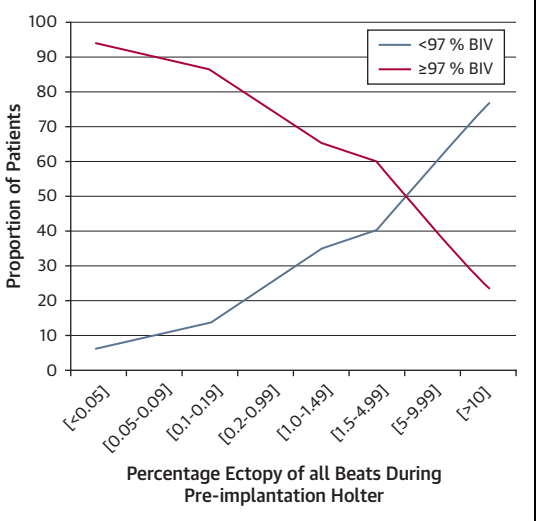


FIGURE 2 Distribution of Patients According to Percentage of All Beats That Were Ectopic, Stratified by High and Low BIV Pacing Percentage (≥97% and <97%)

The proportion of patients with low biventricular (BIV) pacing percentage (<97%) increased with increasing ectopic burden. In patients with very low ectopic burden, the majority of patients achieved a biventricular pacing percentage ≥97%.

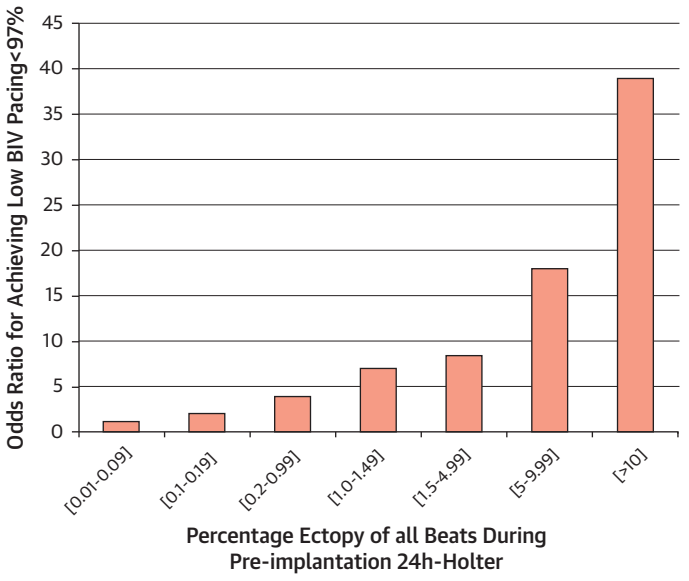


FIGURE 3 Likelihood of Attaining Low BIV Pacing Percentage (<97%) by Increasing Ectopic Burden

Odds ratios of receiving low biventricular (BIV) pacing percentage (<97%) compared with higher (≥97%) in a multivariate logistic regression model. Model adjusted for age, left bundle branch block, prior ventricular arrhythmias, prior myocardial infarction, and creatinine levels. Increasing ectopic burden resulted in higher likelihood of low BIV pacing percentage. CI = confidence interval.

beats than in those with <0.1% ectopic beats (OR: 6.79; CI: 3.64 to 12.68; p < 0.001).

When we evaluated APCs and PVCs separately, it was evident that the ectopic burden of APCs alone independently increased the likelihood of low pacing by 9% per percent increase in APC burden (OR: 1.09; 95% CI: 1.02 to 1.16; p = 0.015), whereas an increase in PVC burden increased the likelihood by 22% per percent increase in PVC burden (OR: 1.22; 95% CI: 1.16 to 1.28; p < 0.001). Because of the left skew in ectopic distribution, we additionally used an ordinal scale by 0.1% in the range 0% to 1.5% and showed that few subtle changes in ectopic burden increased the likelihood of low biventricular pacing by 16% per 0.1% increase in ectopic beats (OR: 1.16; 95% CI: 1.13 to 1.19; p < 0.001).

A total of 609 patients underwent the 1-year follow-up echocardiogram and thus had paired 1-year analyses with baseline measurements. The echocardiographic measured reductions in LVESV and left ventricular end-diastolic volume were significantly greater in patients who had a low amount of ectopic beats. Patients with ≥0.1% ectopic beats had significantly less reverse remodeling (reduction in LVESV 31 ± 15%) than patients with <0.1% ectopic beats (reduction in LVESV 39 ± 14%; p < 0.001). The same was evident for changes in LAV and left ventricular ejection fraction. (Figure 4 shows all 3 ectopic groups.) In addition, patients with a low (<0.1%) percentage of ectopic beats were significantly more likely to be super-responders (defined as >30% reduction in LVESV), with 78% of the patients experiencing super-response in LVESV. Patients with 0.1% to 1.5% ectopic beats were super-responders in 57% of the cases, whereas those with >1.5% ectopic beats had a super-response in 50% of the cases.

Long-term outcomes by ectopic burden are shown by Kaplan-Meier graph (Figure 5A) and the multivariate Cox regression model in Table 3. Patients with a low or very low (<0.1%) frequency of ectopic beats had a significantly more favorable outcome, with a cumulative probability of HF hospitalization or death as low as 5% at 4-year follow-up. Patients with 0.1% to 1.5% ectopic beats had an unfavorable outcome compared with those in the lowest group, with a significant 3-fold relative increase in risk of HF hospitalization or death (hazard ratio: 3.13; CI: 1.40 to 7.02; p = 0.005). There was a negligible increase in risk of HF or death evident among the patients who had the highest amount of ectopic beats (>1.5%) compared with the middle ectopic beat group (Table 3, Figures 5A and 5C). The linear relation in risk of HF or death up to a cutoff of 1.5% ectopic beats was evident, with an 8% increase in HF or death for each 0.1% increase in ectopic beats. As also shown in Table 3, the increased risk of HF/death was driven by HF hospitalizations and primarily by the ectopic burden of PVCs. There was no significant increase in

TABLE 2 Association Between Number of Ectopic Beats (Ectopic Burden) and Likelihood of Low BIV Pacing (<97%) Versus High Percentage (≥97%)

	Odds Ratio: BIV Pacing <97% vs. BIV Pacing ≥97%	95% CI	p Value
Per percent increase in ectopic beats	1.18	1.14–1.23	<0.001
Per 0.1% increase in ectopic beats*	1.02	1.01–1.02	<0.001
<0.1% ectopic beats (<85 total APCs or PVCs)	1.00 = ref	NA	NA
0.1%–1.5% ectopic beats (85–1,347 total APCs or PVCs)	3.37	1.74–6.50	<0.001
>1.5% ectopic beats (>1,347 total APCs or PVCs)	13.42	7.02–25.66	<0.001
Separate analysis of APCs and PVCs			
Per percent increase in APCs/total beats	1.09	1.02–1.16	0.015
Per percent increase in PVCs/total beats	1.22	1.16–1.28	<0.001

Multivariate logistic regression model. Adjusted for age, left bundle branch block QRS configuration, prior ventricular arrhythmias, prior myocardial infarction, and creatinine level. *If estimated by use of an ordinal scale in the range from 0% to 1.5% by 0.1% increase and pooling patients with more than 1.5% ectopy: odds ratio: 1.16; 95% CI: 1.13 to 1.19; p < 0.001 per 0.1% increase in ectopic beats.

CI = confidence interval; NA = not applicable; ref = reference; other abbreviations as in Table 1.

HF/death by burden of APCs alone, despite the separate influence of APCs on biventricular pacing percentage. Also, there was no significant association between ectopic burden and all-cause mortality.

We further assessed the risk of VTAs, which were significantly associated with an increasing percentage of ectopic beats. The cumulative 4-year event rates were 10%, 20%, and 31% in the 3 groups, respectively, as shown in **Figure 5B**, which was confirmed in multivariate analysis shown in **Table 3**. The risk of VTAs by increasing ectopic burden was driven by the influence of PVCs. APCs were not independently associated with increased risk of VTAs.

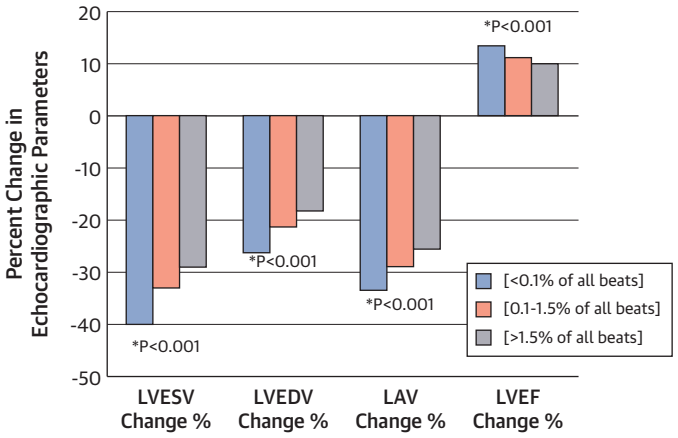


FIGURE 4 Echocardiography-Measured Changes at 1-Year Follow-Up by Ectopic Burden During Pre-Implantation 24-h Holter Monitoring in Cardiac Resynchronization Therapy Patients

Increasing baseline ectopic burden resulted in less reverse remodeling as measured by 1-year changes in left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), left atrial volume (LAV), and left ventricular ejection fraction (LVEF).

DISCUSSION

In this analysis, we aimed to determine whether a high burden of ectopic beats attenuated the probability of high biventricular pacing and whether ectopic beats affected reverse remodeling and long-term outcome. The major findings from this study are that patients who have a relatively low burden of ectopic beats, as low as 1 in 1,000 beats as identified by pre-implantation 24-h Holter recordings, are more likely to attain low biventricular pacing, as well as adverse echocardiographic reverse remodeling parameters and clinical outcomes (**Central Illustration**). Pre-implantation Holter monitoring also identified a patient subgroup (<0.1% ectopy) with a very high likelihood of achieving high biventricular pacing and with favorable reverse remodeling and clinical outcomes. The patients who had a low prevalence of ectopic beats also had other pre-implantation characteristics for favorable response in reverse remodeling and clinical outcomes. At baseline, these patients had many prerequisites already known to result in superior response: female sex, LBBB QRS configuration, lower age, and wider QRS configurations. Likewise, the ventricular and atrial volumes measured by echocardiography at baseline were somewhat larger in patients with high percentages of ectopic beats. Despite this, the relative reductions at 1-year follow-up echocardiographic volumes were significantly smaller in these patients than in the patients with the lowest percentage of ectopy. Our study is further confirmatory of the well-known association of PVCs and the risk of future sustained VTAs and progression of HF. However, this study uniquely assessed the probability of obtaining high biventricular pacing and the link to changes in echocardiographic parameters.

The frequency of APCs and PVCs varies significantly depending on the characteristics of the study population. In our population, the ectopic burden was dominated by PVCs, and 50% of the patients experienced >490 PVCs, whereas the median number of APCs was only 28. A total of 40% of the patients had >1,000 PVCs, which is slightly less than but comparable to the results of a smaller study (n = 102 patients in NYHA functional class II and III) (14), in which 48% of the patients had >1,000 PVCs. In our study, we found some important differences in clinical characteristics associated with higher prevalence of ectopic beats. Frequent PVCs were much more common among the elderly, in males, in those with ischemic cardiomyopathy, and in those with dilated ventricles, which is consistent with reports on characteristics of nonsustained ventricular tachycardia from SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (15), CHF-STAT (Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy) (16), and GESICA-GEMA (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina-Grupo de Estudios Multicéntricos en Argentina) (17).

PVCs can worsen or cause HF, and this association has been determined in many studies. PVCs are associated with a decrease in both diastolic and systolic function. The causal relationship, whether PVCs are a result of underlying cardiomyopathy or can contribute to cardiomyopathy or both, is not well established. In HF patients, however, PVCs have been shown to be an independent marker of subsequent malignant VTAs and sudden cardiac death (18–20). In

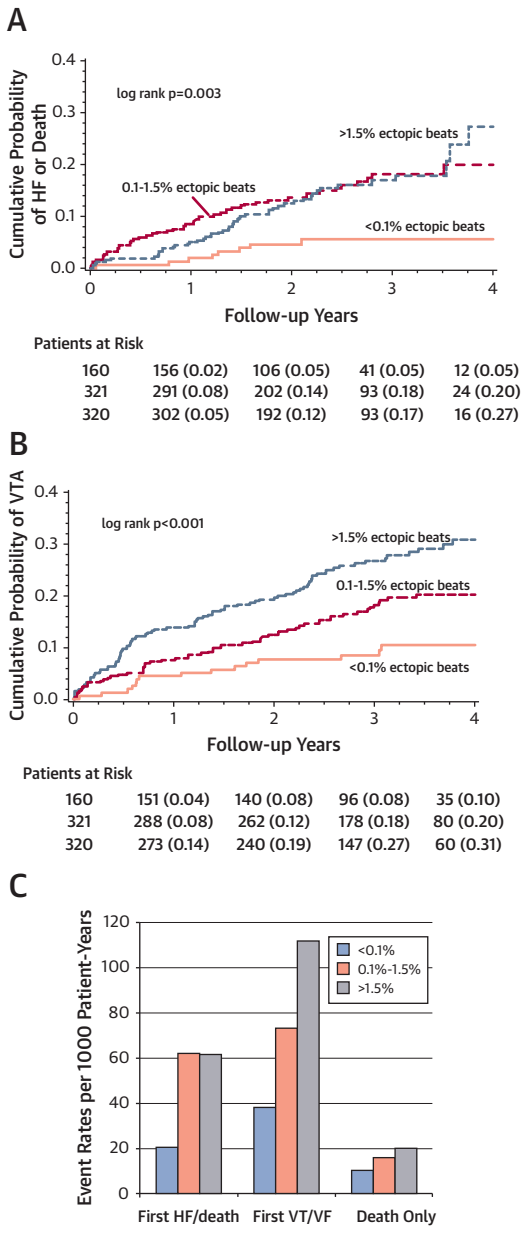


FIGURE 5 Kaplan-Meier Estimates of Primary Endpoint of Hospitalization for HF or Death and Secondary Endpoint of Hospitalization for VTAs, and Event Rates of Total HF or Death Events and Total VTAs, by Ectopic Burden at Pre-Implantation 24-h Holter Monitoring

(A) An increasing ectopic burden (>0.1%) resulted in a significantly increased risk of heart failure (HF)/death compared with <0.1% ectopic beats. No significant difference was found between groups with 0.1% to 1.5% ectopic beats and those with >1.5% ectopic beats for risk of HF/death. **(B)** An increase in the number of ectopic beats was significantly associated with increased risk of ventricular tachyarrhythmia (VTA). **(C)** An increase in the amount of ectopic beats resulted in an increased risk of HF/death with no further increase in event rates for >1.5% ectopic beats compared with 0.1% to 1.5% ectopic beats. VF = ventricular fibrillation; VT = ventricular tachycardia.

this study of mild HF patients, we found PVCs and ectopic beats were not only independent markers of future hospitalizations for HF or death and VTAs but also significantly associated with less reverse remodeling, a lower probability of super CRT response, and a higher probability of low biventricular pacing. Causality is difficult to establish in this type of retrospective study, but there appears to be a direct link between an inability to obtain a high biventricular pacing percentage because of high burden of ectopic beats and the subsequent adverse outcome.

The mechanism by which PVCs and APCs attenuate biventricular pacing and worsen outcome is complex and multifactorial. PVCs have a deleterious effect on the clinical course of patients with HF in general, because they impair cardiac output and may reflect electrical instability in the myocardium or a myocardial arrhythmogenic "substrate" and thus may be a marker of impending malignant VTAs (18–20). These effects in combination with increased sympathetic activity and possible proarrhythmic medications all contribute to adverse outcomes. However, PVCs also interfere with effective biventricular pacing through several other mechanisms; a PVC that inhibits a paced beat may result in resetting of the post-ventricular atrial refractory period, such that the next sinus atrial electrogram is ignored and not sensed. Further loss of ventricular capture and inappropriate long atrioventricular-delay programming are factors that inhibit biventricular pacing in the presence of PVCs. Further PVCs increase intraventricular dyssynchrony, which interferes with delivery of effective biventricular pacing and promotes deterioration of left ventricular function.

APCs, although not as frequent a contributor as PVCs to reduced biventricular pacing, may inhibit optimal biventricular pacing through various degrees of fused beats by intrinsic conduction and may be a marker of later runs of clinically unrecognized atrial fibrillation, as has been shown in the general population (21). For atrial fibrillation, this may lead to irregular ventricular responses (R-R irregularity). An irregular ventricular response results in increased sympathetic nerve activity, which may promote VTAs and worsen the clinical course. Atrial-ventricular irregularity and loss of coordination also cause worsening of mitral regurgitation and a loss of the atrial contribution to cardiac output and exacerbate heart failure symptoms (22). Permanent atrial fibrillation has been associated with lower rates of high biventricular pacing and adverse outcomes (5,23,24). We found that an increasing burden of APCs increased the likelihood of low biventricular pacing

TABLE 3 Multivariate Cox Regression Analysis of Endpoint of Hospitalization for HF or Death, VTAs, and Death Alone

		HF/Death				VTAs				Death Only			
	n	Events	Hazard Ratio*	95% CI	p Value	Events	Hazard Ratio†	95% CI	p Value	Events	Hazard Ratio‡	95% CI	p Value
Per 0.1% increase in ectopic beats§	NA	NA	1.08	1.01–1.15	0.020	NA	1.05	1.02–1.07	0.039	NA	0.99	0.93–1.05	0.70
<0.1 % ectopic beats <85 total APCs or PVCs	160	8	1.00 = ref	NA	NA	15	1.00 = ref	NA	NA	4	1.00 = ref	NA	NA
0.1%–1.5% ectopic beats 85–1,347 total APCs or PVCs	321	51	3.13	1.40–7.02	0.005	60	1.84	1.04–3.28	0.037	13	1.00	0.32–3.15	0.99
>1.5% ectopic beats >1,347 total APCs or PVCs	320	49	2.38	1.04–5.42	0.039	89	2.74	1.56–4.82	0.001	16	0.82	0.25–2.65	0.74
Separate analysis of APCs and PVCs													
Per 0.1% increase in APCs§	NA	NA	1.01	0.84–1.21	0.96	NA	1.01	0.98–1.05	0.46	NA	0.98	0.91–1.07	0.69
Per 0.1% increase in PVCs§	NA	NA	1.08	1.02–1.15	0.016	NA	1.05	1.02–1.07	<0.001	NA	1.00	0.95–1.06	0.94

*Adjusted for female sex, ischemic cardiomyopathy, left bundle branch block (LBBB), worst New York Heart Association (NYHA) functional class = III, left ventricular ejection fraction (LVEF), and creatinine level. †Adjusted for female sex, ischemic cardiomyopathy, LBBB, prior ventricular arrhythmias, LVEF, and non-U.S. enrolling centers. ‡Adjusted for female sex, ischemic cardiomyopathy, LBBB, worst NYHA class III, LVEF, and creatinine level. §Estimated by use of an ordinal scale in the range from 0% to 1.5% by 0.1% increase, and pooling patients with more than 1.5% ectopy as a linear relation was no more evident for heart failure/death above this cutoff for ectopic beats.

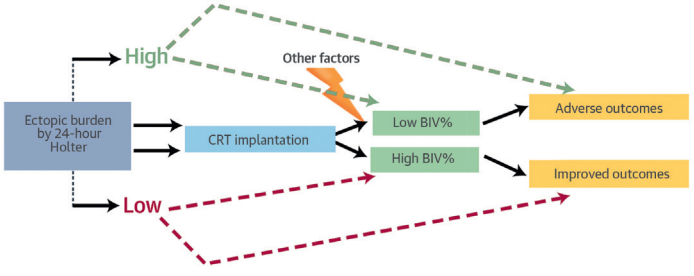
VTA = ventricular tachyarrhythmias; other abbreviations as in Table 2.

by 9% per percent increase in APC ectopic burden, which supports an important role of APCs as a factor to be considered when one evaluates the biventricular response. On the other hand, we did not find any evidence that APCs were independently associated with adverse outcome. That a decreased probability of high biventricular pacing by an increasing amount of APCs translates into HF events is therefore speculative.

The cumulative incidence of HF/death (8 events in 160 patients) in the group with low ectopic burden was found to be even lower than a previously developed risk score that selected the highest quartile of CRT responders and estimated outcome (3-year rate of 11%), as previously done in the MADIT-CRT population (25), which indicates that a very low ectopic burden is a robust marker of very low risk in HF patients. The 4-year cumulative incidence of HF/death with >1.5% ectopic beats reached similar rates as in the original ICD-only cohort from the MADIT-CRT population (4-year rate of 35%) (1). The rather low cumulative incidence of VTAs in this group not only denotes the association between ectopic burden and risk of VTA but also implies a reduction in VTAs by higher rates of biventricular pacing percentage, which remains to be explored in detail.

Using quantification of ectopic beats before implantation, we were able to identify a large group of HF patients with a very low event rate of hospitalization for HF/death, as well as malignant ventricular tachyarrhythmias. Furthermore, these patients experienced a high probability of achieving a high biventricular pacing percentage. We were able to distinguish and specify that even rather infrequent ectopic beats in the range of 0.1% to 1.5% were significantly associated with clinical deterioration and reduced response in reverse remodeling, as well as a lower probability of high biventricular pacing percentage. This suggests the use of pre-implantation Holter monitoring for selection of patients for optimization of CRT and risk stratification of HF patients and supports aggressive treatment of PVCs to enhance biventricular optimization.

STUDY LIMITATIONS. We had no information on physician-initiated therapies or the indications for therapy for high burdens of ectopic beats. In some cases, patients may have been treated more aggressively with antiarrhythmic medications, ablation procedures, changes in atrioventricular delay, or other CRT programming optimizations, or in other ways may have been handled differently from those



CENTRAL ILLUSTRATION High Frequency of Atrial and Ventricular Ectopic Beats

High frequency of atrial and ventricular ectopic beats measured by 24-h Holter recording is associated with reduced biventricular (BIV) pacing percentage and adverse outcomes. CRT = cardiac resynchronization therapy.

with low burdens of ectopic beats to accommodate the high burden of PVCs. Furthermore, this is a post-hoc analysis, and although the statistical models take many confounders into account in the multivariate models, there may be unmeasured confounding influence on the results. In particular, patients with low amounts of ectopy generally were less sick and had many of the characteristics known to be associated with CRT response, such as LBBB QRS morphology, nonischemic cardiomyopathy, and female sex. In the multivariate analysis for the endpoints of HF/death, VTA, and death, we adjusted for factors that were significantly associated with the outcome, but other unknown imbalances between the ectopic groups may have affected the results.

CONCLUSIONS

Pre-implantation 24-h Holter monitoring can identify CRT patients with a higher probability of low biventricular pacing. An increasing number of ectopic beats is associated with low biventricular pacing, less reverse remodeling, and adverse clinical outcome. Similarly, it identifies patients with a very low number of ectopic beats, <1 in 1,000, who are very likely to obtain high biventricular pacing and who have a very low risk of adverse outcomes. Holter monitoring can help identify patients unlikely to respond to CRT, and this study suggests that patients with frequent APCs or PVCs should be followed up closely so that measures can be taken to optimize biventricular pacing.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The presence of a high percentage of biventricular paced beats reduces the risks of death or hospitalization for heart failure in patients with reduced left ventricular ejection fraction and wide QRS complexes.

COMPETENCY IN PATIENT CARE: Patients with ≥0.1% ectopic beats often have <97% biventricular paced beats and are at higher risk of developing decompensated heart failure, ventricular arrhythmias, or death.

TRANSLATIONAL OUTLOOK: Among patients with implanted cardiac resynchronization devices, evaluation of the frequency of ectopic beats by 24-h Holter monitoring can identify those likely to have a high percentage of biventricular pacing who will have improved clinical outcomes. Prospective studies will be necessary to evaluate whether patients identified by this method will benefit from more aggressive antiarrhythmic therapy.

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